GASTRIC ESOPHAGEAL REFLUX DISEASE:

DEFINITION:
- Condition that develops when the reflux of gastric content causes troublesome symptoms or complications
- Heartburn & regurgitation are principal symptoms of GERD
  - Heartburn = burning sensation in chest or upper abdomen
  - Regurgitation = perception of gastric contents in mouth or hypopharynx
- Acid reflux is most common cause of heartburn

TYPES OF REFLUX DISEASE:
1) Esophageal (30%):
   - Reflux esophagitis
   - Reflux strictures
   - Barrett’s esophagitis
   - Esophageal adenocarcinoma
2) Absence of esophageal lesions (70%):
   - Nonerosive reflux disease (NERD)

REFLUX DISEASE AND PAIN:
- Only about 50% of acid reflux episodes seem to evoke pain
  - Low pH activates chemoreceptors to evoke pain
  - Severity of pain increases as pH lowers
    - pH of 6 can evoke pain in 40% of patients
  - Loss of mucus barrier activates nociceptors (TRPV1 receptor) → esophageal distension and sustained esophageal contractions → heartburn pain through activation of mechanoreceptors
  - Stress increases perception of heartburn and may act to alter esophageal mucosal barriers
  - Chronic exposure to low pH, bilirubin, proteases & mechanical stimuli sensitize the esophagus, lowering pain thresholds
  - ACh and pain:

<table>
<thead>
<tr>
<th>Edrophonium</th>
<th>Atropine</th>
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<tbody>
<tr>
<td>Short-acting cholinesterase inhibitor that increases cholinergic mediated esophageal (and GI) smooth muscle contractions and increases gastric acid secretion</td>
<td>Muscarinic receptor antagonist that inhibits cholinergic mediated esophageal contractions and also decreases gastric acid secretion</td>
</tr>
</tbody>
</table>

= Increased pain sensitivity
= Decreased pain sensitivity

TREATMENT OF ESOPHAGITIS:
- Esophageal healing can be achieved with acid neutralization
  - Antacids, H2 antagonists, PPIs
    - PPIs are most effective agents for treatment (symptomatic relief in 70-80% of patients)
  - Symptoms recur after discontinuation of all treatment
  - Intermittent courses for recurrent symptoms required
- Prokinetic agents (speed gastric emptying) used mainly in combination with PPIs or H2 blockers in patients with regurgitation or refractory heartburn
  - Symptom severity (pain, heartburn) correlates poorly with presence and severity of esophagitis
  - Symptoms can persist despite healing of lesions

PEPTIC ULCER DISEASE:

TYPES OF ULCERS:
- Duodenal ulcers are 4 times more common than gastric ulcers
- Duodenal ulcers occur in young adults, gastric ulcers in older adults
- Both types of ulcers are more common in men

SYMPTOMS:
- Epigastriic pain relieved by food intake or antacids
- Pain between meals and/or that causes awakening at night
- Loss of appetite and weight loss

MORE SEVERE ULCERATION:
- Anemia, hematemesis, melena, hemepositive stool = maybe bleeding
- Severe radiating pain = maybe perforation (→ peritonitis)

MUCUS-BICARBONATE-PHOSPHOLIPID “BARRIER”:
- Prostaglandins (PGE2, PGI2) enhance gastric mucosal protection by:
  - Stimulating mucus production
  - Bicarbonate secretion (EP1 receptor)
  - Epithelial cell proliferation
  - Increasing mucosal blood flow

CAUSES:

<table>
<thead>
<tr>
<th>Mucosal damage</th>
<th>Stomach &amp; proximal duodenum most common</th>
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<tbody>
<tr>
<td>H. pylori infection (50%)</td>
<td>H pylori found in stomach of 50% of population</td>
</tr>
<tr>
<td></td>
<td>Infection leads to gastritis which disrupts acid homeostasis</td>
</tr>
<tr>
<td></td>
<td>Increases gastrin levels (more H+ production)</td>
</tr>
<tr>
<td></td>
<td>Decreases gastric mucus production</td>
</tr>
<tr>
<td></td>
<td>Decreases duodenal mucus bicarbonate secretion = favors ulcer formation</td>
</tr>
<tr>
<td></td>
<td>Eradication of infection reduces ulcer recurrence</td>
</tr>
<tr>
<td>NSAIDs (5-20% on long-term therapy)</td>
<td>Inhibits cyclooxygenase, decreasing levels of prostaglandins (= decreased gastric mucosal production)</td>
</tr>
<tr>
<td></td>
<td>Can co-exist with H pylori infection = increase risk of ulceration</td>
</tr>
<tr>
<td>Stress</td>
<td>Critical illness, surgery or hypovolemia → splanchic hypoperfusion → stress ulcers</td>
</tr>
<tr>
<td>Smoking</td>
<td>Exacerbates and slows healing</td>
</tr>
</tbody>
</table>

TREATMENT OF PEPTIC ULCER DISEASE:

<table>
<thead>
<tr>
<th>Ulcers</th>
<th>PPIs heal &gt; 90% duodenal (4 wk) and gastric (6-8 wks) ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.pylori</td>
<td>10-14 day regimen of “triple therapy” (PPI, clarithromycin and amoxicillin or metronidazole), then PPI x 4-6 weeks</td>
</tr>
<tr>
<td>NSAID</td>
<td>Discontinue NSAID</td>
</tr>
<tr>
<td></td>
<td>PPIs reduce incidence of ulcers &amp; ulcer complications in pts taking aspirin or other NSAIDs</td>
</tr>
<tr>
<td>Stress</td>
<td>PPIs and H2 antagonists (similar efficacy)</td>
</tr>
<tr>
<td></td>
<td>Mucosal protective agents (sucralfate)</td>
</tr>
</tbody>
</table>
### Lecture 4

#### PROTAGOLANDIN ANALOGUES
- Misoprostol
  - Prostaglandin derivative that is cytoprotective and inhibits gastric acid secretion
  - EP (EP1 & EP3) receptors responsible for its actions
  - Used for prevention of NSAID-induced peptic ulcers

#### MUCOSAL PROTECTIVE AGENTS
- Sucralfate
  - Mechanism of Action:
    1. Sucrose complexed to sulfated aluminum hydroxide \( \rightarrow \) breaks down into sucrose sulfate (strongly negatively charged)
    2. Binds to +ve proteins in base of ulcer and forms a physical barrier that restricts further damage
  - Uses:
    - Administered as slurry through nasogastric tube to reduce stress ulcers in pts at risk from infxn
    - Avoids use of antacids, H2 antagonists or PPIs
  - Adverse Effects:
    - Not absorbed = few systemic AEs
    - Constipation occurs rarely

#### POTASSIUM:
- (K+)
  - Anti-cholinergic properties
  - Also an antispasmodic

#### ANTACIDS:
- Non-prescription remedies for treatment of intermittent heartburn and dyspepsia
- Antacids = weak bases that react with gastric HCl to form a salt and water (which then neutralizes acid)

#### SODIUM BICARBONATE (baking soda):
- Reacts rapidly with HCl to produce CO2 and H2O
- Results in gastric distension and belching
- High doses may cause metabolic alkalosis

#### CALCIUM CARBONATE:
- Slow reaction with HCl to form CO2 and CaCl2
- May cause belching or metabolic alkalosis

#### MAGNESIUM HYDROXIDE \& ALUMINUM HYDROXIDE:
- React slowly with HCl to form magnesium chloride or aluminum choride and water
- No gas is generated = no belching
- Metabolic alkalosis is also uncommon
- Combination preferred because:
  - Unabsorbed magnesium salts may cause osmotic diarrhea
  - Aluminum salts may cause constipation
  - Al and Mg absorbed and excreted by kidneys = problem in renal failure
  - Salts bind many drugs and iron

#### POTASSIUM-COMPETITIVE ACID BLOCKERS (P-CABs):
- Soraprazan, revaprazan, vonoprazan
- Compete with K+ for binding site on proton pump
- Fast onset of action, full effect with 1st dose
- May have greater acid suppression than PPIs

#### DOPAMINE D2 RECEPTOR ANTAGONISTS:
- Metoclopramide & domperidone
  - DA receptors inhibit cholinergic smooth muscle stimulation
    - Blockade of D2 receptors enhances effect of ACh release to increase:
      - esophageal peristaltic amplitude & sphincter, pressure & gastric emptying
      - Can also be used for impaired gastric emptying
    - No effect upon small intestine or colonic motility
  - Metoclopramide may also block D2 receptors in CRTZ (nausea & antiemetic)

#### ADVERSE EFFECTS OF H2 ANTAGONISTS:
- 3% get diarrhea, headache, fatigue, myalgias or constipation
- Confusion, hallucinations, agitation may occur in ICU or elderly patients
- Bradycardia occurs as a result of blocking H2 receptors, but rarely clinically important
  - Can occur with rapid IV infusion
  - Agents cross placenta and accumulate in breast milk

#### PROKINETIC AGENTS:
- Drugs that stimulate gut motor function and/or improve gastric emptying
  - Muscarinic agonists, dopamine D2 antagonists, 5-HT4 receptor agonists (Cisapride)

#### DOPAMINE D2 RECEPTOR ANTAGONISTS:
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#### ADVERSE EFFECTS:
- Metoclopramide: CNS (restlessness, drowsiness, insomnia, anxiety, agitation, EPS)
- Domperidone: well-tolerated (does not cross the BB)
- Both: elevate prolactin levels & may cause breast tenderness and enlargement, galactorrhea (uncommon) and menstrual irregularities (including amenorrhea)